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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,797	12/17/2003	Katherine Meyer Siegler	111828-00109	7390

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1643	

MAIL DATE	DELIVERY MODE
07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/644,797	SIEGLER, KATHERINE MEYER	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-93* is/are pending in the application.

4a) Of the above claim(s) *6-10,16-22 and 24-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 11-15, and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070521*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 21, 2007, has been entered.

1. The amendment filed May 21, 2007, is acknowledged and has been entered. Claim 1 has been amended.

2. Claims 1-93 are pending in the application. Claims 6-10, 16-22, and 24-93 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 9, 2006.

3. Claims 1-5, 11-15, and 23 are currently under prosecution.

Information Disclosure Statement

4. The information disclosure filed May 21, 2007, has been considered. An initialed copy is enclosed.

Grounds of Objection and Rejection Withdrawn

5. Applicant's amendment and/or arguments submitted May 21, 2007, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed February 28, 2007.

Response to Arguments

6. Applicant's arguments with respect to the grounds of rejection set forth in the previous Office action mailed February 28, 2007, have been considered, but are moot in view of the new ground of rejection that follows.

New Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-5, 11-15, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required

in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The claim is directed to a method for detecting or diagnosing prostate cancer in an individual by the active step of determining levels of MIF in the serum of the individual, wherein if serum MIF levels fall within the range of greater than about 5 to about 10 ng/ml, the presence of prostate cancer in the individual is indicated.

However, while the intended use of the claimed invention is to detect or diagnose prostate cancer, it would appear that the claimed process, per se, would not necessarily achieve that objective, even in instance where serum MIF levels of greater than about 5 to about 10 ng/ml are found, because identical levels of MIF are present in the sera of individuals that are not afflicted with prostate cancer. For example, Mitamura et al. (*Br. J. Ophthalmol.* 2000; **84**: 636-639) (of record) teaches a process comprising measuring the levels of MIF in the serum of individuals, which resulted in a determination that MIF levels in the sera of patients with proliferative diabetic retinopathy and controls fell within the specified range of between about 5 and 10 ng/ml (i.e., 7.17 and 5.76 ng/ml, respectively); see, see entire document (e.g., the abstract; page 638, column 1). Similarly, Leech et al. (*Arthritis Rheumatol.* 2000 Apr; **43** (4): 827-833) (of record) teaches a process comprising measuring the levels of MIF in the serum of individuals, which as evidenced by Mitamura et al. (cited *supra*), resulted in a determination that MIF levels in the sera of patients with proliferative diabetic retinopathy and controls fell within the specified range (7.17 and 5.76 ng/ml, respectively); see, e.g., page 638, column 1. Then, Zhang et al. (*Hepatobiliary Pancreat. Dis. Int.* 2002 Nov; **1** (4): 577-580) (of record) teaches a process comprising measuring the levels of MIF in the serum of individuals, which resulted in a determination that MIF levels in the sera of control patients that again fell within the specified range (i.e., 4.06 ± 0/71 ng/ml), although the levels of MIF in the sera of patients diagnosed with liver disease (i.e., chronic hepatitis or hepatitis cirrhosis with or without ascites) were substantially elevated above the level in the control sera; see entire document (e.g., the abstract; and page 578, Table).

Therefore, there is factual evidence that the practice of the invention, which, as presently claimed, is indistinguishable from manipulatively identical processes disclosed by the prior art (e.g., Mitamura et al. [*supra*]) for assessing the occurrence in the individual of wholly different conditions or diseases (e.g., proliferative diabetic retinopathy), cannot be used to achieve the claimed objective or that purpose which is intended, since the prior art teaches numerous individuals that, despite having MIF levels in the requisite range, were *not* afflicted with prostate cancer.

This evidence suggests that though there might be a correlation between the level of MIF in the sera of individuals afflicted with prostate cancer, it cannot be suffice to measure the level of MIF in the serum of the individual alone, so as to enable the practitioner to detect or diagnose prostate cancer, because the presence of identical levels of MIF also correlates with the absence of disease and/or the presence of very different conditions or diseases.

This position is further supported by additional observations that have been reported. For example, Maaser et al. (*Gastroenterology*. 2002 Mar; **122** (3): 667-680) (of record) teaches ubiquitous production of MIF by gastric and intestinal epithelium. He et al. (*Gut*. 2006; **55**: 797-802) (of record) teaches increased epithelial and serum expression of MIF in gastric cancer. Kitaichi et al. (*Graefe's Arch. Clin. Exp. Ophthalmol.* 2006; **244**: 825-828) (of record) teaches MIF expression in lacrimal fluid of patients with severe atopic dermatitis. Chen et al. (*Am. J. Trop. Med. Hyg.* 2006; **74** (1): 142-147) (of record) teaches serum levels of MIF in patients infected by dengue viruses. Kibiki et al. (*Clin. Immunol.* 2007; in press; copy of electronically published document, pp. 1-6) (of record) teaches serum and BAL MIF levels in patients infected with HIV. Rahman et al. (*Annals Surg.* 2007 Feb; **245** (2): 282-289) (of record) teaches serum MIF is a marker of pancreatic necrosis. Yanagi et al. (*Cytokine*. 2006; **35**: 270-274) (of record) teaches MIF is a proinflammatory cytokine present in the serum of patients afflicted with contact dermatitis. Collectively these data that have been reported in the literature suggest that serum MIF may be a general marker of inflammation and immune response, which is associated with a great number of normal conditions, as well as pathologies of disparate etiologies, rather than a marker of any one specific disease, such as prostate cancer.

Indeed, Michael et al. (*Prostate*. 2005; **62**: 34-39) (of record) notes that MIF was first described almost 40 years ago, originally characterized as a product of T lymphocytes, whereas

today MIF is known as an ubiquitously expressed cytokine with varied functions including regulation of inflammatory and immune response, cell proliferation, angiogenesis, and the expression of tumor suppressor genes (page 35, column 1).

It is perhaps for the very same reason that Michael et al. (*supra*) reports the finding of the diagnostic invalidity of serum MIF in patients with prostate cancer; see entire document (e.g., the abstract). Michael et al. found that concentrations of serum MIF in healthy men and men afflicted by benign prostate hyperplasia (BPH) did not differ, whereas the mean value of serum MIF in patients afflicted by prostate cancer was significantly decreased, and notably falling below the requiste level that is recited in the claims; see, e.g., the abstract. Furthermore, although PSA is an established marker for prostate cancer, Michael et al. found no correlation between the level of serum MIF and PSA; see, e.g., the abstract. Moreover, after prostatectomy, while PSA levels contiunously decreased, as might be expected following surgical resection of the cancer, Michael et al. noted that serum levels disconcordantly increased; see, e.g., the abstract. Finally, Michael et al. determined that analyses of reciever operating curves (ROCs) and logistic regressioins did not show that serum MIF alone, or any tested MIF related variables (i.e., MIF/tPSA; (fPSA x MIF); (fPSA x MIF)/tPSA) could improve specificity or sensitivity of measuring total PSA to detect prostate cancer in individuals; see, e.g., the abstract.

Similar results have been more recently reported by Stephan et al. (*Prostate*. 2006; 66: 651-659), leading Jung and collegues to the draw the same conclusion that serum MIF alone has limited value as a marker of prostate cancer; see entire document (e.g., page 657, paragraph bridging columns).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
July 16, 2007